REMARKS

Claims 1-7 and 18-19 are pending in this application. Entry of the remarks is respectfully requested.

Pending Claims are Patentable over Muller in view of Tobinick and D'Amato

Claims 1-7 and 18-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,020,358 to Muller et al., in view of U.S. Patent No. 6,428,787 to Tobinick and U.S. Patent No. 6,235,756 to D'Amato. (Office Action, pages 3-4). Applicant respectfully disagrees.

In *KSR International Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385, 1395 (2007) (emphasis added). According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, the guidelines for the examination of patents in the wake of the *KSR* decision make clear that an Examiner may still apply the TSM test, after resolution of the *Graham* analysis. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57528 (Oct. 10, 2007) ("USPTO Guidelines").

1. The PTO has failed to make a *prima facie* case of obviousness.

The *Graham* factual inquiries are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR,* 82 U.S.P.Q.2d at 1395 (*citing Graham,* 383 U.S. at 15-17). Once the *Graham* factors have been addressed, the Examiner may apply the TSM test, asking whether (1) a teaching, suggestion or motivation exists in the prior art to combine the references cited, and (2) one skilled in the art would have a reasonable expectation of success. *See* USPTO Guidelines at 57534.

The *Graham* factual inquiries begin with an analysis of the scope and content of the prior art, in view of the scope of the claimed invention. *See* USPTO Guidelines

at 57527 (*citing Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005)). The instant claims recite, *inter alia*, methods of treating a specific disease, macular degeneration, with a specific compound, cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide.

The prior art cited by the Examiner consists of Muller et al, Tobinick and D'Amato. Muller teaches the use of substituted phenethylsulfones for reducing TNF-α level. Muller does not disclose or suggest the use of the specific compound for treating macular degeneration as recited in the instant claims.

Tobinick provides no teaching or suggestion of the specific compound of the instant claims. Tobinick relates to, and focuses on specific antibodies and their uses in treating a number of diseases. Tobinick teaches treating conditions of the optic nerve or retina by administering a TNF antagonist for reducing the inflammation of neuronal tissue, or for modulating the immune response affecting neuronal tissue. In Tobinick, the TNF antagonist is selected from the group consisting of etanercept, infliximab, pegylated soluble TNF receptor Type I (PEGsTNF-R1), CDP571 (a humanized monoclonal anti-TNF-alpha antibody), and D2E7 (a human anti-TNF mAb). This teaching can hardly be said to focus on small molecule compounds, isoindoline-containing molecules, much less on the recited compound of the instant claims. One skilled in the art would be taught of the merits of using the antibodies disclosed therein. One skilled in the art reading Tobinick would not be motivated to use any small molecule compound instead of the antibodies. Therefore, Tobinick does not provide any teaching, suggestion or motivation to select the specific compound as recited in the instant claims, to treat macular degeneration.

D'Amato does not cure the deficiency of Muller and Tobinick. D'Amato fails to disclose or suggest a method of treating macular degeneration using cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide, as an essential agent, as recited in the instant claims. D'Amato discloses compounds of generic formula for use in treating undesired angiogenesis. The genus disclosed in D'Amato encompass millions of compounds. (*See* Column 6-12 and Figures 1-5). There is no teaching or suggestion in D'Amato to select the compound recited in the instant claims from the vast number of compounds covered by the generic formula. A disclosure of a broad genus encompassing millions of compounds does not render a claim of a species obvious. *In re Baird,* 16 F. 3d 380 (Fed. Cir. 1994). Moreover, the instant claims recite not the

species *per se*, but the use of the species, which is not disclosed nor preferred by D'Amato, in specific methods using a specific compound in a specific patient population against a specific disease. D'Amato is simply devoid of any such teachings.

In fact, D'Amato teaches away from the selection of the recited compound by focusing on the uses of compounds different from that recited by the present claims. The examples in D'Amato disclose that five compounds were tested for inhibition of angiogenesis: thalidomide, EM-12, phthaloyl glutamic anhydride, phthaloyl glutamic acid and supidimide. (*See* Column 16-17 and Figures 6-7). Thus, D'Amato teaches away to an extent that it points to the uses of different species from the recited compound. In other words, the teaching concerning other species, or compounds of general formula suggests nothing about the compound used in the claimed methods. Thus, D'Amato does not provide any suggestion or motivation for the selection of the recited compound.

Further, in the context of claims to chemical compounds and their biological properties, the Federal Circuit has recently applied the TSM test under 35 U.S.C. § 103. *See Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350 (Fed. Cir. 2007). In *Takeda*, the Court held that the compounds at issue were not *prima facie* obvious over structurally similar "compound b" of the prior art because the prior art provided no motivation to modify compound b to arrive at the claimed compounds, and there was no reasonable expectation that the modification would provide the desired pharmacological properties. *Id.* at 1360. Indeed, the court noted that "we have cautioned 'that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.'" *Id.* at 1361 (*quoting In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985)). Thus, the current law of obviousness in cases concerning structurally similar compounds "requires a showing of 'adequate support in the prior art' for the change in structure." *Id.* at 1356 (*quoting In re Grabiak*, 769 F.2d at 729).

As was the case in *Takeda*, there is no showing of support for the change in structure from the compound of the prior art (in this case, e.g., thalidomide), to the compound of the instant claims. Applicant respectfully points the Examiner to *Takeda*, in which the court found that a change from a methyl group at the 6-position of a compound to an ethyl group at the 5-position was not *prima facie* obvious. *Id.* at 1359. In stark contrast to the facts of *Takeda*, the structural changes required to make

cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide from thalidomide require the complete removal of one of four different carbonyl groups, and the additions of cyclopropyl carboxamide group at one of four positions on the aromatic ring and 2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl group. The references cited by the Examiner provide no guidance for these changes. Moreover, unlike the homologous substitution of methyl for ethyl in *Takeda*, any number of different substituents could have been selected to replace the hydrogen in thalidomide. As the Court held in *Takeda*, the prior art cited by the Examiner does not provide a "finite number of identified, predictable solutions," but a "broad selection of compounds any of which could have been selected as the lead compound for further investigation." *Id.* at 1359. *See also In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *Grabiak,* 769 F.2d 729, 731-32 (Fed. Cir. 1985) ("There must be adequate support in the prior art for the prior art ester/thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."); *In re Lalu,* 747 F.2d 703, 705 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.").

Therefore, in view of the current law of obviousness, the Examiner has not provided adequate support in the prior art for the instant change in structure. *See Id.* at 1356. For these reasons alone, a *prima facie* case of obvious cannot be made.

2. One skilled in the art would have no reasonable expectation of success to arrive at the instant claims in view of the teachings of the cited references.

Further, the references cited by the Examiner do not suggest to one of ordinary skill in the art that the present invention would have a reasonable expectation of success. To have a reasonable expectation of success, "one must be motivated to do more than merely 'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave...no direction as to which of many possible choices is likely to be successful.'" *Medichem, S.A. v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Furthermore, the courts have long recognized the

unpredictability of biological properties of chemical compounds. *See In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."); *see also Takeda*, 429 F.3d at 1361.

Muller is silent as to the treatment of macular degeneration as claimed herein. Tobinick merely discloses that TNF-α inhibiting antibodies may be used to treat various conditions by TNF-α inhibition. The specific compound of the instant claims is not taught or suggested in Tobinick. From the combination of Muller and Tobinick which teaches away from small molecule compounds, one skilled in the art would have no reasonable expectation that the specific compound of the instant claims would be useful to treat a specific disease, macular degeneration .

D'Amato does not cure this defect. As described above, D'Amato does not disclose the specific compound of the instant claims, cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide for use in macular degeneration. D'Amato discloses a generic formula, or the uses of EM-138, thalidomide, EM-12, phthaloyl glutamic anhydride, phthaloyl glutamic acid and supidimide as examples, which are different from the recited compound. As is known to one skilled in the art, even slight modifications in structure of compounds can have substantial effects on the properties of a compound. Further, alleged obvious differences in specific chemical structures must be adequately supported in the prior art. *See* Takeda at 1361 and *In re Grabiak*, at 731-32. Thus, one skilled in the art would not be able to predict whether the recited compound in the present claims would be useful to treat macular degeneration in view of the teachings of the cited references.

Simply put, to arrive at the methods of the instant claims, one skilled in the art must "vary all parameters or try each of numerous possible choices" of the cited references without "direction as to which of many possible choices is likely to be successful." *Medichem*, 437 F.3d at 1165. This is precisely what the courts have held not to be a reasonable expectation of success. *Id.*; *O'Farrell*, 853 F.2d at 903-04.

Because the PTO has not demonstrated that one skilled in the art would have had a reasonable expectation of success in practicing the methods of the instant claims by combining the teachings of the references, the Examiner has failed to state a *prima facie* case of obviousness. Therefore, the instant claims are not obvious.

CONCLUSION

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Please apply any charges or any credits, to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: January 10, 2008

Yeah-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778